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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/421,971	10/20/1999	FRED H. GAGE	SALK2350	4863

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/421,971	GAGE ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-11, 13-22 are pending and under consideration.

Response to Amendment and Arguments

Applicant's arguments filed 05/24/2004 have been fully considered but they are not persuasive for the reasons set forth below.

New issues are also set forth below.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a chimeric protein comprising a fusion of EcR-USP/RXR into a functional dimer, does not reasonably provide enablement for chimeric proteins comprising two functional protein units wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, for reasons of record set forth in the Office Action of 12/24/2003. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection of record set forth that claims 1-11, 13-22 are overly broad since they encompass functional dimers comprising any member of the steroid/thyroid hormone nuclear receptor superfamily, which are set forth on page 13 line 19 to page 14, line 23 of the

specification. The claims thus encompass dimers comprising, inter alia, glucocorticoid receptors, mineralocorticoid receptors, estrogen receptor, progesterone receptor, androgen receptor, vitamin d3 receptor, retinoic acid receptors, farnesoid X receptors etc., as well as members of this superfamily from any animal. Applicant has provided an example wherein a chimeric protein comprising a fusion of EcR-USP/RXR into a functional dimer was made. However, the art recognizes that the nuclear hormone receptor superfamily is a large and complex family, (see Aranda A, Pascual A. Nuclear hormone receptors and gene expression. Physiol Rev. 2001 Jul;81(3):1269-304). The Aranda reference teaches that the exact biochemical mechanisms by which these receptors stimulate transcription are still unclear (page 1296, first column). The Aranda reference further teaches that the superfamily is subdivided into six distinct subfamilies (page 1271, column 1, fourth paragraph). The Aranda reference further teaches that there are functional differences within the superfamily, for example, the receptors can bind as monomers, homodimers or heterodimers see page 1275, column 2, first and second paragraphs. Furthermore, the claims encompass members of the superfamily that are orphan receptors, for which no ligand is known (page 1272, Table 1).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. While the claims set forth a functional limitation for the chimeric polypeptides wherein the polypeptide can bind DNA, bind ligand, transactivate or dimerize, as taught by the Aranda reference, the exact biochemical mechanisms by which these receptors stimulate transcription are still unclear, and additionally, the encompassed proteins differ in the function, in that some form dimers, while some function as monomers. Furthermore, since the ligand for many of the

encompassed protein are unknown, one of skill in the art would not be able to test for the ligand binding function. Since detailed information regarding the structural and functional requirements of the polypeptide are lacking, it is unpredictable as to which of the encompassed proteins, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polypeptides that the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for chimeric proteins comprising two functional protein units wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, and has not taught how to make chimeric proteins comprising two functional protein units wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

Applicant argues that they have provided more than a reasonable amount of guidance with respect to any experimentation required to carry out the present invention, with respect to the functional protein units, one of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine appropriate domains to assemble in the

construction of a chimeric protein in order to achieve one or more biological functions, and that Example 1 teaches the complete design and construction of exemplary chimeric fusion constructs.

Applicant further argues that the reference cited by the Examiner, Aranda, in fact supports enablement of the full scope of the present claims. Aranda states that like other transcriptional regulators, nuclear receptor exhibit a modular structure with different regions corresponding to autonomous functional domains that can be interchanged between related receptors without loss of function.

However, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In the instant case the claims do not contain any structural information regarding the claimed protein, and only set forth functional language by which the protein can be identified, and as established above, the protein art is unpredictable. The claims encompass a large number of possible proteins, and in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the

construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. Here, the examples provided are of fusion protein comprising Ecr and RXR, while the claims encompass functional dimers comprising any member of the steroid/thyroid hormone nuclear receptor superfamily. The Aranda reference established that the nuclear hormone receptor superfamily is a large and complex family, and that there are functional differences within the superfamily. Thus, the claims lack enablement for their full scope since only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim.

Claims 1-11, 13-22 stand rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the Office Action of 12/24/2003. Applicant is directed to the Guidelines for the Examination of Patent Applications

Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. The claims encompass functional dimers comprising any member of the steroid/thyroid hormone nuclear receptor superfamily, which are set forth on page 13 line 19 to page 14, line 23 of the specification. The claims thus encompass dimers comprising, inter alia, glucocorticoid receptors, mineralocorticoid receptors, estrogen receptor, progesterone receptor, androgen receptor, vitamin d3 receptor, retinoic acid receptors, farnesoid X receptors etc., as well as members of this superfamily from any animal. The specification and claims do not indicate what distinguishing attributes shared by the members of the genus. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide sufficient guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a chimeric protein comprising a fusion of EcR-USP/RXR functional dimer is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical

properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed (see see Aranda A, Pascual A. Nuclear hormone receptors and gene expression. Physiol Rev. 2001 Jul;81(3):1269-304). The Aranda reference teaches that the exact biochemical mechanisms by which these receptors stimulate transcription are still unclear (page 1296, first column). The Aranda reference further teaches that there are functional differences within the superfamily, for example, the receptors can bind as monomers, homodimers or heterodimers see page 1275, column 2, first and second paragraphs. Furthermore, the claims encompass members of the superfamily that are orphan receptors, for which no ligand is known (page 1272, Table 1). Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure

fails to provide a representative number of species to describe the genus, thus, applicant was not in possession of the claimed genus.

Applicant argues that this superfamily contains a remarkably uniform domain structure that was known in the art at time of filing of the present application. Applicant additionally argues that the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. Applicant further argues that clearly, the specification provides more than ample description of the conserved region of the members of the receptor superfamily, in addition to the knowledge of one of skill in the art.

Here, the claims are drawn to a protein, but there is no structure set forth for the protein, only a function is set forth. However, in University of California v. Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. the Court decided that a definition by function alone "does not suffice" to sufficiently describe a biomolecule "because it is only an indication of what the gene does, rather than what it is." Further, "it is only a definition of a useful result rather that a definition of what achieves that result...The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention". *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14, 19, 20, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Lees et al. (1990), as evidenced by Peters et al. (1999).

The claims are drawn to a fusion protein comprising two subunits, each of which is at least a dimerization domain of a steroid hormone receptor, and wherein the fusion protein has an activity selected from DNA binding, ligand binding and dimerization. The claims are anticipated by the Lees reference because the Lee reference teaches the production of a fusion protein comprising an estrogen receptor dimerization domain fused to constructs of the ER comprising parts of the B, C and D domains, and part of the E domain (see page 5530, Figure 2, MOR89-384DM). This meets the limitations of the claims because the construct comprises two functional units, one of which it's the ER dimerization domain, and the other comprises the DNA binding domain. The DNA binding domain is known in the art to have a weak dimerization activity itself (see Lees, page 5529, column 1, second paragraph; and also see the Peters reference, page 286, column 2, second paragraph). The MOR89-384DM construct of Lees et al.

meets the limitations of the claims because it is a fusion protein comprising two subunits, each of which is at least a dimerization domain of a steroid hormone receptor, and wherein the fusion protein has an activity selected from DNA binding, ligand binding and dimerization

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
August 5, 2004

JOSEPH MURPHY
PATENT EXAMINER